U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug Administration

Data Request (DR001): Use of the pH Cycling Test Model as a Testing Procedure for Fluoride Dentifrice Drug Products in Over-the-Counter (OTC) Monograph M021: Anticaries Drug Products for Over-the-Counter Human Use

(Issued July 28, 2026)

I. Introduction

The Food and Drug Administration (FDA) is announcing this Data Request for the submission of data from the public to help inform whether the pH cycling test model should be included as a testing procedure for fluoride dentifrice drug products under Over-the-Counter (OTC) Monograph M021: Anticaries Drug Products for Over-the-Counter Human Use (OTC Monograph M021).

II. Submitting Data

A. Dates

Submit data on this request electronically by 11:59 p.m. at the end of January 25, 2027. Data submitted after this time will not be considered.

B. Instructions

Data must be submitted electronically. The Federal eRulemaking Portal https://www.regulations.gov will accept data submissions at any time until 11:59 p.m. Eastern Time at the end of January 25, 2027.

Submit data electronically as follows:

- Federal eRulemaking Portal: https://www.regulations.gov. To submit data, follow the instructions in the Federal eRulemaking Portal for submitting comments. All data submissions must include the Docket No. FDA-2026-N-7864 for "Data Request (DR001): Use of the pH Cycling Test Model as a Testing Procedure for Fluoride Dentifrice Drug Products in Over-the-Counter (OTC) Monograph M021: Anticaries Drug Products for Over-the-Counter Human Use."

- Electronic data submissions, including attachments, to https://www.regulations.gov will generally be posted to the docket unchanged, subject to redactions of confidential information as discussed below, and subject to FDA's review of content that may have copyright protections.

- Confidential Submissions: For data submissions with confidential information that you do not wish to be made publicly available, electronically submit two copies of the data as an attachment to your submission. One copy will include the information that you claim to be confidential with a heading or cover note that states, "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." FDA will review this copy, including the claimed confidential information, in its consideration of the data submission. The second copy, which will have the claimed information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov.

- Additionally, your data submission should not include any information that you or a third party may not wish to be publicly posted, such as medical information or your or anyone else's Social Security number. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- FDA will place the data submissions that are submitted in a timely manner (see Dates and Instructions) in the docket. FDA intends to make these data submissions publicly viewable on https://www.regulations.gov at the time that any proposed order that the data submission helped inform is issued under section 505G(b) of the FD&C Act (21 U.S.C. 355h(b)). Any information marked as "confidential" will not be disclosed except in accordance with section 505G(d) of the FD&C Act, and other applicable disclosure laws. In addition, the administrative order process is generally a public process. Therefore, FDA may not be able to rely on certain confidential information with respect to such a proposed order unless the submitter consents to the disclosure.

C. Contact Information

For further information, contact: Michael Boblitz, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-002, 301-837-7651.

III. Background

A. OTC Monograph Drug Regulation

Section 505G of the FD&C Act (21 U.S.C. 355h) sets forth the framework for the regulation of over-the-counter (OTC) monograph drugs. OTC monograph drugs may be marketed without a new drug application approved under section 505 of the FD&C Act (21 U.S.C. 355) if they meet the requirements of section 505G of the FD&C Act, as well as other applicable requirements. An OTC monograph set forth in a final order under section 505G for a therapeutic category of drugs describes the conditions, such as active ingredients, uses (indications), doses, routes of administration, labeling, and testing, under which OTC monograph drugs within such therapeutic category are generally recognized as safe and effective (GRASE) for their intended use. The conditions described in an OTC monograph may be amended, revoked, or otherwise modified in accordance with a final order issued under section 505G(b) of the FD&C Act. Either FDA or a

requestor[1] can initiate the order process in section 505G(b). A requestor can initiate the order process by submitting an OTC monograph order request (OMOR)[2] with respect to certain drugs, classes of drugs, or combinations of drugs. FDA may opt to request data and information from the public to help inform future OTC monograph activities, including development of an FDA-initiated proposed order under section 505G (see 91 FR 43647 (July 16, 2025)).

B. Anticaries Drug Products for OTC Human Use

OTC Monograph M021 describes the conditions under which OTC anticaries drug products are GRASE. OTC Monograph M021 is set forth in Final Administrative Order OTC000034[3] as deemed established by section 505G(b)(8) of the FD&C Act and effective upon enactment of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act), Public Law 116-136, on March 27, 2020.

Under the conditions set forth in OTC Monograph M021, fluoride dentifrice drug products[4] must comply with testing procedures in § M021.70 of OTC Monograph M021. This final formulation testing demonstrates formulation effectiveness for the fluoride dentifrice drug products. Fluoride dentifrice drug products must meet the biological test requirements for animal caries reduction and one of the following tests: (1) enamel solubility reduction; or (2) fluoride enamel uptake[5] (see § M021.70(a) of OTC Monograph M021). An alternative testing procedure may be used. The proposed procedure must be submitted to FDA by a requestor in an OMOR, or by any other interested party in a citizen petition. The submission should contain data to support the modification or data demonstrating that the alternative testing procedure provides results of equivalent accuracy (see § M021.70(c) of OTC Monograph M021).

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[1] Under section 505G(q)(3) of the FD&C Act (21 U.S.C. 355h(q)(3)), the term *requestor* refers to any person or group of persons marketing, manufacturing, processing, or developing an OTC monograph drug.

[2] An OTC monograph order request (OMOR) means a request for an order submitted under section 505G(b)(5) of the FD&C Act (see section 744L(7) of the FD&C Act).

[3] Final Administrative Order OTC000034 Over-the-Counter (OTC) Monograph M021: Anticaries Drug Products for Over-the-Counter Human Use is available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

[4] In this document, a fluoride dentifrice drug product refers to fluoride dentifrice drug products that meet each condition described in § M021.10 of OTC Monograph M021, including the active ingredients and their respective concentrations.

[5] These biological testing procedures for fluoride dentifrices are under the Supporting Documents tab for Final Administrative Order OTC000034 available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

C. pH Cycling Test Model

Scientific advancements have led to the development of the pH cycling test model, which is a nonanimal model that may be a suitable testing procedure for OTC fluoride dentifrice drug products (Refs. (1-4)) The pH cycling test model exposes tooth specimens to three phases: (1) a test dentifrice treatment; (2) an acidic demineralizing solution that mimics the periods of demineralization[6] in the mouth after a high carbohydrate meal; and (3) a neutral remineralizing solution that mimics saliva and remineralization periods in the mouth. The tooth specimens are cycled through the dentifrice treatment, demineralization, and remineralization phases for several days and net demineralization of the tooth specimens is measured at the end of the experiment (Ref. (3)). These phases mimic biologic processes that occur in the mouth that contribute to caries formation and measure the role of dentifrice treatment in preventing tooth demineralization.

Although different pH cycling test models (Refs. (1), (3)) exist, published pH cycling test protocols lack standardization. The only published validation attempt (Ref. (5)) did not use a standardized protocol at each validation site, and results between study sites were not reproducible. Published pH cycling test models exhibit methodological variations in numerous critical parameters including specimen preparation, solution compositions, cycling conditions, and evaluation techniques (Refs. (1), (3)).

D. Purpose of Data Request

FDA is considering whether there is sufficient scientific justification to issue an order that, once final, would amend OTC Monograph M021 in accordance with section 505G(b) of the FD&C Act to add the pH cycling test model as a nonanimal testing procedure for fluoride dentifrice drug products.

Therefore, we seek data from interested parties and the public generally to inform whether the pH cycling test model is a suitable testing procedure for OTC fluoride dentifrice drug products. FDA included its intention to issue this data request in the annual forecast posted September 2, 2025.[7]

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[6] Demineralization dissolves minerals from tooth enamel when oral pH drops below approximately 5.5, releasing calcium and phosphate ions. Acids come from plaque bacteria metabolizing sugars and from acidic foods/beverages. Remineralization is the repair process where minerals from saliva are redeposited into enamel as pH returns to neutral. Fluoride enhances this process by combining with hydroxyapatite, the mineral component of enamel to form fluorapatite; because fluorapatite forms at a lower pH than 5.5, it allows the remineralization process to begin earlier after an acid challenge and it results in a more acid-resistant mineral structure than hydroxyapatite. Tooth decay develops when demineralization consistently exceeds remineralization, progressively weakening enamel and leading to caries.

[7] The annual forecast is a nonbinding list, issued each year, of planned OTC monograph activities that FDA intends to initiate over the ensuing 3 years. The annual forecast, last posted on September 2, 2025, is available via the OTC Monographs@FDA portal at https://www.accessdata.fda.gov/scripts/cder/omuf/.

IV. Data Request and Issues for Consideration

A. Data Request

In considering the addition of the pH cycling test model as a testing procedure for fluoride dentifrice drug products to OTC Monograph M021, FDA is seeking data on the following:

1. A standardized protocol for the pH cycling test model that addresses the issues described in Section IV.B. Issues for Consideration.
2. Results of at least one multisite validation study from a standardized protocol of pH cycling test model. Include a detailed analysis of the results and complete datasets with full distributional details rather than summary data alone.
3. Results from completed pH cycling studies utilizing the standardized, validated protocol compared with results of previously completed animal caries reduction test, and any additional supportive data or information. Include a detailed analysis of the method's ability to separate effective from ineffective dentifrice formulations that includes a comparison of pH cycling test data generated in at least one multi-site study to existing animal caries reduction test data supported by complete datasets with full distributional details.

FDA encourages interested parties to request a meeting with FDA to discuss any development program for pH cycling test models, including test dentifrice formulations and protocol design,[8] prior to generating or submitting such data.

Alternatively, a requestor may consider the submission of an OMOR requesting that FDA issue an order to add the pH cycling test model as a final formulation testing procedure to demonstrate dentifrice effectiveness.[9] FDA encourages requestors to meet with FDA to discuss the potential submission of an OMOR.

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[8] For sponsors and requestors of OTC monograph drugs under section 505G of the FD&C Act, see the draft guidance for industry *Formal Meetings Between FDA and Sponsors or Requestors of Over-the-Counter Monograph Drugs* (February 2022). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. For interested parties that are not sponsors or requestors of OTC monograph drugs, see FDA's Professional Affairs and Stakeholder Engagement (PASE) website to obtain information on requesting a meeting, available at https://www.fda.gov/about-fda/cder-offices-and-divisions/office-communications-professional-affairs-and-stakeholder-engagement-pase-staff.

[9] See section 505G(b)(5) of the FD&C Act (21 U.S.C. 355h(b)(5)). The OMOR must be submitted to FDA in the form and manner specified by the Agency (see sections 505G(b)(5)(B) of the FD&C Act (21 U.S.C. 355h(b)(5)(B)). FDA will file the OMOR if FDA determines that the OMOR is sufficiently complete and formatted to permit FDA to conduct a substantive review (see section 505G(b)(5)(A) of the FD&C Act). See also the draft guidance for industry *Over-the-Counter Monograph Order Requests: Format and Content* (April 2023). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fdaguidance-documents.

B. Issues for Consideration

FDA has identified issues that we recommend be evaluated as part of the development and validation of the protocol for the pH cycling test model and addressed in the data submitted to FDA. In your data submission, include your evaluation of the following issues and provide supporting data and information to explain your rationale:

1. Tested Dentifrices

To be included in OTC Monograph M021, the pH cycling test model would need to be validated for all active ingredients and at the specified concentrations range for each active ingredient in § M021.10 of OTC Monograph M021. A pH cycling test model would need to demonstrate a dose-response across the theoretical total fluorine dose ranges and the respective available fluoride ion concentrations specified in § M021.10.

a. Identify the foreseeable limitations in pH cycling test models based on the dentifrice characteristics, if any. Include a discussion of limitations and impacts from: (1) the active ingredient; (2) total theoretical fluorine or available fluoride ion concentration; and (3) abrasives used.

b. Discuss how any limitations would be addressed in the pH cycling test model protocol.

c. For each dentifrice used, specify the active ingredient, the abrasive, the total theoretical fluorine content, and available fluoride ion concentration.

2. Specimen Selection

The pH cycling test models discussed in the literature include various types of tooth specimens: human or other species (Refs. (5-7)), primary (Ref. (8)) or permanent (Ref. (9)) dentition, enamel (Ref. (5)) or dentin (Ref. (10)), and other varieties. FDA recommends the use of enamel specimens from permanent human teeth as the most physiologically relevant specimens.

a. Discuss how the pH cycling test model is designed to control for variations in the type of tooth selected as the specimen, enamel thickness, specimen source, and donor demographic factors such as fluoride exposure, diet, and age. Include in your discussion: (1) the baseline measurement and inclusion/exclusion criteria necessary to ensure a balanced distribution of specimen characteristics; and (2) the tooth specimen selection criteria necessary to minimize variability in enamel characteristics. If the protocol does not employ baseline measurements, include a rationale that is supported by scientific data and/or peer-reviewed scientific literature.

3. Sample Preparation and Sectional Cutting of the Teeth

To be included in OTC Monograph M021, the pH cycling test model would need to employ standardized sample preparation steps. Published pH cycling studies used enamel samples derived from a range of tooth specimens including whole crowns (Ref. (9)), half crowns (Ref. (11)), quartered crowns (Ref. (12)), enamel blocks (Ref. (13)), enamel cores (Ref. (14)), and other geometries such as slabs.

a. Identify the specimen preparation methods that ensure consistent surface characteristics while maintaining physiological relevance. Address the feasibility and practicality of the specimen preparation methods.

b. Address how the testing procedure should standardize specimen surface processing from cleaning to polishing.

c. Identify the enamel specimen geometries (e.g., whole or half crown, slabs, cores) that optimize reproducibility.

4. Demineralization-Remineralization Cycling

Some pH cycling test models measure net demineralization (Refs. (3), (5), (15)) while others measure net remineralization (Refs. (3), (16)). FDA recommends that net demineralization models be used to best assess the drug product's effectiveness in the prevention of dental caries.

a. Identify the demineralizing and remineralizing solution compositions that ensure efficient demineralization levels across different specimen types.

b. Identify the cycling duration, frequency, temperature, and solution refreshment schedules that are optimal for establishing a standard pH cycling test model.

c. Identify the net demineralization models that are physiologically relevant to the indication for caries prevention in OTC Monograph M021.

5. Determination of Lesion Size

Evaluation techniques that can be used to assess tooth specimen integrity include: microradiography (Ref. (17)), microscopy (polarized light microscopy) (Ref. (18)), scanning electron microscopy (Ref. (19)), computed tomography (Ref. (13)), fluorescence-based testing (Refs. (12, 16)), vibrational spectroscopy (Refs. (20)), and microhardness testing (Ref. (5)).

a. Identify the evaluation techniques that most accurately measure tooth specimen integrity before and/or following the demineralization-remineralization pH cycling phase. Include comments on how practical, economical, readily available and feasible these techniques are.

b. Within microhardness testing, variations include surface (Ref. (6), (21)) or cross-sectional (Refs. (5), (13)) microhardness. If proposing to use microhardness testing, discuss how surface versus cross-sectional microhardness evaluation techniques compare in providing an understanding of the treatment impact on enamel mineralization. Discuss to what extent protocols should standardize microhardness parameters including diamond type, indentation depth, load mass, and lesion measurement.

c. Discuss what role, if any baseline measurements should play in reducing the variability of the treatment effect estimates.

6. Statistical Analysis

Biological tests must use the United States Pharmacopeia (USP) fluoride dentifrice reference standards (see § M021.70(b) of OTC Monograph M021). As part of the biological tests, a test dentifrice is compared with a clinically effective positive control USP reference dentifrice. Therefore, the pH cycling test model should also include statistically sound comparisons to the USP reference dentifrice and appropriate negative controls to ensure th002at the test dentifrice is effective and meets the biological test requirements. Specifically, the hypothesis testing framework should be designed to demonstrate that the test dentifrice is superior to the negative control and not inferior to the USP reference dentifrice (i.e., that the test dentifrice has a treatment effect greater than an appropriate fraction of the USP reference dentifrice treatment effect). To minimize bias and promote interpretable results, a standardized pH cycling test model protocol should adhere to statistical principles of randomization, blinding, use of appropriate control arms, prespecification of endpoints and analysis methods, appropriate missing data handling, and adequate control of type I error.

a. Discuss the predicted barriers with implementing these statistical principles into pH cycling test models.

b. Discuss other statistical factors the agency should consider when establishing a standardized method.

c. Discuss how the specific statistical hypotheses should be defined in the testing framework.

d. Identify sample sizes that ensure adequate power for key hypothesis tests comparing test dentifrices to USP reference standards and negative controls.

7. Method Validation

Validation studies of a test method demonstrate the method's reliability by obtaining reproducible results across multiple study locations using a standardized protocol across each location. To support inclusion of the pH cycling test model in OTC Monograph M021, the validation study would need to demonstrate that the pH cycling test model following a standardized protocol, evaluated across multiple test sites, can reliably distinguish between products with meaningfully different fluoride levels. Validation studies should evaluate fluoride dose responses across low, intermediate, and high concentrations for each active ingredient to measure product's effectiveness across the theoretical fluorine and available fluoride ion dose ranges in § M021.10 of OTC Monograph M021.

a. Identify validation study designs for the pH cycling test model.

b. Identify pilot testing strategies that can optimize protocol parameters before conducting adequate and well-controlled validation studies.

V. References

The following references are not on public display at https://www.regulations.gov because they have copyright restrictions. Some may be available at the website address, if listed. References are available for viewing only at the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. These references are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.

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